REMARKS

Applicants file this Request for Continue Examination to further present their positions to the Examiner in view of the Final Office action issued on November 22, 2004.

The application was originally filed with claims 1-28. In a Response to a restriction requirement, claims 1-10 and Compound 10113 were elected for continue prosecution and claims 11-28 were withdrew from consideration. In response to Examiner's First Office Action, claims 2-4, 6 and 8 were cancelled and claims 29-32 were added. Claims 29-32 were added to more specifically point out the scope of the invention. Support for these claims can be found from amended claim 1 and claim 9 from which the new claims depend. In the Final Office, the Examiner rejected claims 1, 5, 7, 9-28; but did not acknowledge the entry of new claims 29-32.

The entry of the previously filed new claims 29-32 is respectfully requested. Upon the entry of the amendments, claims 1, 5, 7, 9, 10 and 29-32 are pending and under examination on the merits.

Applicants thank the Examiner for reviewing the Applicants' remark in the prior response submitted on August 23, 2004. The Applicants acknowledge that the Examiner has withdrawn the rejections of Claims 1-10 under 35 U.S. C. §103(a) as being unpatentable over Wheelhouse *et al.*

Applicants inform the Examiner that at the time the invention in this application was made, U.S. Patent Application No. 09/880,125, now U. S. Patent No. 6,916,799, and the present application have one common inventor, Ines Batinic-Haberle, and are commonly owned by Duke University. The '125 application claims priority to U.S. Patent Application No. 09/184,982, now

abandoned, was filed on November 3, 1998; the Application was assigned to Duke University on November 1, 1999 and the Assignment was recorded with the PTO on Reel 9729 and Frame 0863.

Double Patenting Rejections

The Examiner has rejected claims 1, 5, 7, 9-10 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-51 of copending Application No. 09/880,125, (the '125 application) in view of Kobayashi *et al.* Applicants respectfully inform the Examiner that Application No. 09/880,125 has issued on July 12, 2005 as U. S. Patent No. 6,916,799. The issued patent claims to subject matters similar to those in claims 36-51 of the '125 application. The Applicants anticipate that the Examiner to raise the same objections, and therefore, wish to present their arguments to overcome these rejections.

In making the rejection, the Examiner states:

> '125 claims a method of protecting cell from oxidant, or treating patient with a pathological condition resulting from oxidant-induced toxicity by using pyridine substituted porphyrin.
>
> '125 patent does not expressly teach for treating cancers, or employment the particular compound, 10113.
>
> However, Kobayashi teaches that human cancer patient usually suffer from oxidative stress. Kobayashi *et al.* further teaches to employ superoxide dismutase mimetic for treating cancer patient to relieve the oxidative stress.
>
> Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to use the claim method for treating cancer patient.

> A person of ordinary skill in the art would have been motivated to use the claim method for treating cancer patient because cancer patients are known to have oxidative stress and superoxide dismutase mimetic are known to be useful for treating cancer patient for relief of such oxidative stress. As to the employment of the particular compound, 10113, it is seen to be a selection from amongst equally suitable material and as such obvious. Ex parte Winters 11 USPQ 2nd 1387 (at 1388) (R is ethyl group in 10113 vs. R is C1-C8 in the claims of '125).

See, Final Office Action p. 2, l. 20 to p. 3, l.9.

The Examiner has made the same rejection in a First Office Action mailed on February 23, 2004. The Applicants responded in a communication dated August 24, 2004 contending that Kobayashi *et al.* merely teaches that cancer patients suffer from oxidative stress and reports the results of studies designed to "clarify the mode of action" of a protein-bound polysaccharide of *Coriolus versicolon* QUEL (PS-K) that expresses SOD mimicking activity. *See,* Response to First Office Action, p. 10, ll. 12-17. The Applicants further contended that Kobayashi *et al.* does not teach that treatment of a cancer can be effected by protesting cell from oxidant-induced toxicity, and that Kobayashi *et al.* also does not teach that cancer is a pathological condition resulting from oxidant-induced toxicity. The Applicants then requested that the Examiner to clarify how the cancer treatment method claimed in this application is in any way suggested by the protecting cells from oxidant induced toxicity method of the '125 application. *See,* Response to First Office Action, p. 10, l. 1-3. Applicant further requested the Examiner to clarify how the cancer treatment method claimed in this application is suggested by the treatment of a pathological condition resulting from oxidant-induced toxicity.

In the Final Office Action, the Examiner agrees with the Applicants that "Kobayashi *et al.* does not teach that cancer is a pathological condition resulting from oxidant-induced toxicity." *See,* Final Office Action, p. 9, ll. 2-3. However, the Examiner asserts:

> But Kobayashi *et al.* teach oxidative stress is a condition frequently found in cancer patients. The examiner assert it would have been obvious to treating cancer patient because cancer patients are known to have oxidative stress and superoxide dismutase mimetic are known to be useful for treating cancer patient for relief of such oxidative stress.

See, Final Office Action, p. 9, ll. 3-7.

In response to Applicants' assertion that the instant claims are directed to treating cancer, which has not been taught or suggested by the '125 application in view of Kobayashi *et al.* The Examiner alleges that "Applicants [is]sic confusing the concept of treatment of cancer. Note, symptomology treatment of cancer is a treatment of cancer." and that given a broad interpretation of "treating" the claims would read on the treatment of any symptoms arise from cancer, including the oxidative stress. *See,* Final Office Action, p. 8, l.22 to p.9, l. 1 and p. 9, ll. 10-11, respectively.

Applicants respectfully traverse the Examiner's rejection of claims 1, 5, 7, 9-10 under the judicially created doctrine of obviousness-type double patenting. Applicants submit that the Examiner has not established prima facie obviousness. To establish prima facie obviousness, first there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be

a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Because the cited references did not teach or suggest all the elements of the claimed invention, there is no teaching or motivation to combine. Even if the Examiner found suggestion to combine, there is no expectation of success.

Applicants disagree with the broad definition of treating cancer. The Examiner has repeatedly stated that

> A person of ordinary skill in the art would have been motivated to use the claim method for treating cancer patient because cancer patients are known to have oxidative stress and superoxide dismutase mimetic are known to be useful for treating cancer patient for relief of such oxidative stress.

Final Office Action, p. 3, ll. 4-7. This statement concedes that the reference only teaches treatment of "a cancer patient" or of "oxidative stress." The Examiner's own description of the teaching NEVER says the compound would be used to treat "a cancer." Even the Examiner's own description consistently refers to treating "a cancer patient' rather than a cancer. By the Examiner's statement, at most, the references would have been obvious to treat oxidative stress, which could occur in a cancer patient.

The Examiner asserts that a broad reading of "treating" means that the claims "would read on the treatment of any symptoms arise from cancer including the oxidative stress." This interpretation is unreasonable in light of ordinary usage and in light of the specification. Claim terms must be interpreted in view of the specification, of which they are a part. *Merck & Co. v. Teva Pharmaceuticals USA Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003). Where the specification contains nothing to indicate that claim terms are to

be given anything other than their ordinary meanings, the ordinary meaning controls. *Enercon GmbH v. ITC,* 151 F.3d 1376, 1384 (Fed. Cuir. 1998) citing *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753 (Fed. Cir. 1984). The Specification clearly provides that the compounds treat cancer, not symptoms. *See,* for example, the opening sentence of the Detailed Description of the Invention which states "the present invention relates to methods of preventing or treating cancer using low molecular weight antioxidants ... ." Specification, p.7, ll. 14-17. The Specification further discloses that "cancer types amenable to treatment in accordance with the invention include leukemias, myelomas, and solid tumors such as melanomas, lymphomas, sarcomas, and tumors of the lung, breast, prostate and colon." Specification, p.8, ll. 16-18.

Each of the claims of the current application is directed to a method of using certain compounds in "a method of treating cancer." That simply is NOT the same as using such compounds "for treating cancer patient for relief of such oxidative stress." Consider: aspirin is known to treat pain, cancer patients often experience pain, thus it may be "obvious" to treat a cancer patient with aspirin when pain is a symptom, but that does not equate to the use of aspirin "for treatment of a cancer": such a broad interpretation of the term is not reasonable in light of the specification or the ordinary meaning of the term.

At most, the cited prior art might make it obvious to use a compound to treat a cancer patient known to suffer oxidative stress, and at most it provides a reasonable expectation of success for treating oxidative stress. The reference does NOT provide

ANY expectation that the compounds can successfully treat a cancer as the claims require it to do. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 1, 5, 7, 9-10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of Patent Application No. 09/880,125, (the '125 application) in view of Kobayashi *et al.*

Claim Rejections 35 U.S.C. § 103

The Examiner has rejected claims 1, 5, 7, 9-10 under 35 U.S.C. § 103(a) as being obvious over copending Application No. 09/880,125, which has a common assignee with the instant application, in view of Kobayashi *et al.* The Examiner further rejected claims 1, 5, 7, 9-10 under 35 U.S.C. § 103(a) as being obvious over Kobayashi *et al.* in view of Bloodsworth *et al.*

The obviousness rejection of the present application as unpatentable over U. S. Application No. 09/880,125 in view of Kobayashi *et al.* has been fully discussed in the previous section on Double Patenting Rejection. Applicants respectfully submit that neither the '125 application nor Kobayashi *et al.* teaches the use of superoxide dismutase mimetics to treat cancer; accordingly, the Examiner has not established a prima facie case of obviousness. Applicants request the withdrawal of the rejection of claims 1, 5, 7, 9-10 under 35 U.S.C. § 103(a) as being obvious over copending Application No. 09/880,125 (now US Patent No. 6,916,799) in view of Kobayashi *et al.*

Regarding the rejection of claims 1, 5, 7, 9-10 under 35 U.S.C. 103(a) over Kobayashi *et al.* in view of Bloodsworth *et al.*, the Examiner alleges that Kobayashi *et al.* teaches that mimetics of superoxide dismutase are useful for treating human cancer patients; while Kobayashi

et al. do not teach expressly to employ compound 10113 herein as the mimetic of superoxide dismutase, but Bloodsworth *et al.* teaches that 10113 is a known superoxide dismutase mimetic. The Examiner concludes that it would have been prima facie obvious to a person of ordinary skill in the art at the time the claimed invention was made, to employ 10113 as the superoxide dismutase mimetic in the method for treating cancer patients disclosed by Kobayashi *et al.* A person of ordinary skill in the art would have been motivated to employ 10113 as the superoxide dismutase mimetic in the method for treating cancer patient as disclosed by Kobayashi *et al.* because 10113 is a known super oxide dismutase mimetic. The employment of 10113 as superoxide dismutase mimetic is seen to be a selection from amongst equally suitable material and as such obvious. Ex parte Winters 11 USPQ 2nd 1387 (at 1388).

In response to Applicants' argument that there is no suggestion to combine the references, the Examiner states that

> In this case, the teaching, suggestion, or motivation are found both in the cited references and in the general knowledge available to one of ordinary skill in the art. Particularly, Kobayashi *et al.* teaches the usefulness of superoxide dismutase mimetic for treating cancer. Bloodsworth discloses that compound 10113 is a known superoxide dismutase mimetic. Compound 10113 may differ structurally from the superoxide dismutase mimetics disclosed by Kobayashi. They nevertheless share the same function, and would have been reasonably expected to be similarly useful. In addition, Kobayashi *et al.* never conclusively states superoxide dismutase mimetics are ineffective for treating cancers. In fact, Kobayashi *et al.* provides details suggestion for using the particular superoxide dismutase mimetic for treating cancer.

Final Office, p. 10, lines 3-12.

The Applicants respectfully traverse this rejection. Applicants respectfully submit that Kobayshi *et al.* in view of Bloodsworth *et al.* provides at most the motivation to try the claimed combination, but it does not provide a reasonable expectation of success. It has been previously established that the current application is directed toward methods for treating cancer. The cancers which are amenable to treatment in accordance with the claimed invention include leukemias, myelomas, and solid tumors such as melanomas, lymphomas, sarcomas, and tumors of the lung, breast, prostate and colon. *See,* Specification, p.8, ll. 16-18.

Kobayashi *et al.* gleaned from Shinkai *et al.*, which reports use of reactive oxygen species to promote and/or initiate malignant neoplasma. Kobayashi *et al.* suggests that the protein-bound polysaccharide of *Coriolus vesicolor*, QUEL (PS-K), which express the mimetic activity of superoxide dismutase "may serve to inhibit the progress of malignancy by reducing OS." [OS refers to oxidative stress.] The Shinkai *et al.* reference is not readily available; Applicants thus far have failed in their effort to obtain the article to conduct a full analysis. It is well known, however, that the treatment of cancer is complex. The leap from reports of reactive oxygen species to promote and/or initiate malignant neoplasma to the use of substituted porphyrins SOD to successfully treat cancer is huge. Kobayashi *et al.* offers no evidence, *in vitro* or *in vivo*, that PS-K is effective in treating cancer—only a suggestion that it could work. The only evidence that Kobayashi *et al.* cited to in connection with treatment of cancer using PS-K is the observation "Fukuo *et al.* noted PS-K administered for 7 days prior to cisdiaminedichloroplatinum (cisplatin) therapy to lessen the adverse effect of cisplatin in

cancer patients." *See,* Kobayashi *et al.* p. 58, right hand column. Lessening the adverse effects of a cancer drug is not treating cancer; it is treating a drug side effect. On the other hand, Bloodsworth *et al.* never discusses that SOD mimetics can be used to treat cancer; Bloodsworth *et al.* only teaches the advantageous SOD properties of certain class of metalloporphyrins. Kobayashi *et al.* in view of Bloodsworth *et al.* at best suggests to those skilled in the art that it is reasonable to try the claimed combination; however, obvious to try is insufficient to establish a prima facie case of obviousness. *In re Antonie*, 195 USPQ 6, 8, (CCPA 1977).

Further, those skilled in the art would have no reasonable expectation of success for the combination of Kobayashi *et al.* and Bloodsworth *et al.* It should be noted that the mode of action of the PS-K of Kabayashi *et al.* differs fundamentally from the substituted porphyrins of Bloodsworth *et al.* PS-K is only suitable for short term administration. Kobayashi *et al.* teaches that short term administration of PS-K reduces OS and suppresses the hyper-production of hydroxyl radicals in cancer patients. Increased SOD activity in cancer bearing hosts may bring about the hyper-production of H_2O_2, which leads to inadequate levels of catalase, peroxidase and gulutathione peroxidase with subsequent production of hydroxyl radicals from H_2O_2 through the Fention reaction. *See,* Kobayashi *et al.* p. 58, RH column. Though prolonged PS-K administration caused OS to remain low, plasma LPO gradually increased to a significantly higher level. *See,* Kobayashi *et al.* p. 58, LH column. Excessive hydroxyl radicals would result in increased LPO level which has a detrimental effect on the patient. Kobayashi *et al.* expressly states that "the prolonged administration of PS-K increased

plasma LPO [lipid peroxide] on day 28, and the patent is showed general clinical failure." *See,* Kobayashi *et al.* p. 58, LH column.

The increase of LPO observed in the prolonged use of PS-K would not occur from the prolonged use of the metalloporphyrins SOD mimetics of Bloodsworth *et al.* The metalloporphyrins of Bloodsworth *et al.* can behave as antioxidants not only through free radical scavenging mechanisms, but also by inhibiting lipid oxidation reactions. *See,* Bloodsworth *et al.*, p. 1028. Bloodsworth *et al.* attributes these advantages to the multi-valence states for redox cycling of the substituted metalloporphyrins. The redox state of metalloporphyrins determines rates and extents of reaction with substrates such as O_2^-, H_2O_2, and $ONOO^-$. *See,* Bloodsworth *et al.*, p. 1027. Further, the redox state of metalloporphrins is influenced by the presence of biological reductants *in vivo*. Bloodsworth *et al.* demonstrates that in the absence of reductants, metalloporphyrins, e.g., MnTE-2-PyP^{5+}, promote lipid oxidation through oxidation/reduction reactions concurrent with redox cycling between the Mn^{+3} and Mn^{+4} oxidation state. In the presence of biologically relevant concentrations of reductants (e.g., alpha-tocopherol, ascorbate, and GSH), MnTE-2-PyP^{5+} can limit lipid oxidation by redox cycling between the Mn^{+3} and Mn^{+2} redox states. Thus, Bloodsworth *et al.* shows that during manganese redox cycling between the +2 and +3 states, MnTE-2-PyP^{5+} can serve as an inhibitor of lipid oxidation. *See,* Bloodsworth *et al.*, p. 1028, LH column. The prolonged use of the metalloporphyrins therefore will not have the same detrimental effects experienced from the use of PS-K. The Applicants therefore submit that as a SOD mimetic, the mode of action of PS-K is different from that of the metalloporphyrins; the two classes of SOD are

not obvious, equally suitable materials such that they can be readily substituted for each other. Applicants further submit that, because there they work by different mechanisms, there is no reasonable expectation that the substitution of one class of SOD with another class would be successful, because in the treatment of a complex condition like cancer, when the mechanism of action changes, the result cannot be predicted. Thus a person of ordinary skill in the art would not have had a reasonable expectation of success when trying to use the Bloodsworth metalloporphyrins superoxide dismutase mimetic in the method for treating cancer patent as disclosed by Kobayashi *et al.*

The person of ordinary skill in the art, upon reading the cited references, would at most be motivated to try the claimed combination; and because of the different mechanisms by which the SOD mimetics involved operate, the person could not reasonable expect success with the claimed combination. A hope for success with such a combination is not enough to support an obviousness rejection. Accordingly, the Examiner has not established prima facie case of obvious for the instant claims; Applicants respectfully request the withdrawal of the rejections of claims 1, 5, 7, 9-10 under 35 U.S.C. §103(a) as being unpatentable over Kobayashi *et al.* in view of Bloodsworth *et al.*

CONCLUSION

In view of the above remarks, it is believed that the application is in condition for allowance, and such action is respectfully requested at the Examiner's earliest convenience.

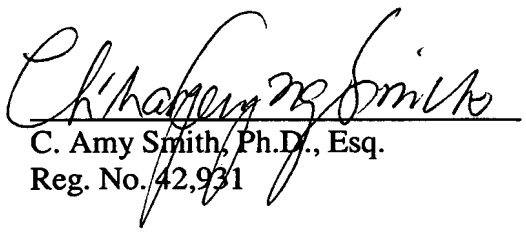
Applicants hereby petition for a 4-month extension of time under 37 CFR § 1.136(a). With the granting of said extension, it is believed that this response is timely filed. The Commissioner is hereby authorized to charge $1,190.00 to Deposit Account No. 50-2613 for the 4-month extension fee due herein and any other fees that may become due or credit become payable during the pendency of this application.

The Examiner is invited to telephone the undersigned, Applicants' attorney of record, to facilitate advancement of the present application.

If the examiner is not persuaded by the remarks and wishes to maintain her rejection to the claims, the Applicants respectfully ask the Examiner to grant a telephonic interview allowing the Applicants to present their arguments in person. Please contact the undersigned to arrange a time that is convenient to the Examiner.

Respectfully Submitted,

Date: October 21, 2005

By: 

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